REMARKS

Amendments to the Claims

Claims 1-9, 12, 13, 19, and 21-24 are pending. No claim amendments are made herein. Accordingly, no new matter has been added.

35 U.S.C. §103

1. Bosch and Kalinski

The Examiner rejects claims 1, 3-5, 9, 18, 19, and 21-24 under 35 U.S.C. §103 as unpatentable over Bosch (U.S. 2005/0059151)(hereinafter Bosch) in view of Kalinski (J. Immunol. 1999, Vol. 162:3231-3236) (hereinafter Kalinski). Applicants respectfully traverse.

Kalinski does not teach a time course of stimulation with LPS/IFN-γ

Applicants herein provide the Declaration of Dr. Germeraad. In the Declaration, Dr. Germeraad explains that Kalinski teaches that the IL-12 achieved in Figure 3 is obtained with a combination of IL-1β/TNF-α or LPS, and CD40/CD40L. (Kalinski, page 3232, col. 1, line 44-48, and legend to Figure 3) The stimulation of immature DCs in Figure 3 with LPS/IFN-γ was for a 24 hour period. (Kalinski, page 3232, col. 1, line 68-70, and legend to Figure 3)

In contrast, the only measure of IL-12 generation in a time course post-maturation is done by Kalinski with IL-1β and TNF-α. Accordingly, Dr. Germeraad explains that the Kalinski methods are different from the present invention, i.e., applying LPS/IFN-γ to immature DCs and obtaining the *timing* of the IL-12 production.

Furthermore, the only stimuli used in the DCs which were matured with IL-1β and TNF-α is CD40L and IFN-γ. Dr. Germeraad explains that the mechanism for IL-12 production based on CD40L is a completely different pathway than the mechanism for IL-12 production with proinflammatory cytokines. In short, when LPS/IFN-γ is applied to immature DCs the timing of IL-12 production is never established.

Accordingly, Dr. Germeraad concludes that Kalinski provides no reason for one of skill in the art to expect that exposing the DCs to LPS and IFN-γ for a limited period of time would produce active DCs.

The prior art does not create a reasonable expectation of success for an in vivo tumor therapy.

Even further, Dr. Germeraad points out that while Kalinski mentions DC loading, it questions the feasibility of such therapies because FCS-free cultures would have to be used. Since the references by Kalinski to an *in vivo* therapy, are speculative, no combination of those teachings with Bosch could provide a reasonable expectation of success. On the other hand, while Bosch would administer the DCs to a human or animal, Bosch provides no explicit teaching that the *in vitro* co-cultivation of DCs described in that paper should be applied as an anti-tumor immune therapeutic *in vivo*. Accordingly, in view of the speculative nature of the applicability of the methods of Kalinski *in vivo*, and the complete absence of an application to a tumor therapy in Bosch, Applicants submit that the Examiner has failed to establish that the combined references teach a method of treatment of a tumor.

One of skill in the art could not expect the efficacy of the present therapy.

Also, as discussed in previous responses, Bosch only teaches that DCs were contacted with BCG and IFN-γ for 24 hours, and are administered as exhausted DCs. As Dr. Germeraad indicates:

> [I]f DCs are matured first for 24 hours or longer and than co-cultivated with T-cells, no more IL-12 production may be detected. Therefore, the claim of Bosch that the observed beneficial effect on T-cell stimulation is due to IL-12 is unsustainable.
>
> The observations may be due to an in vitro artifact: the IL-12 protein secreted from the DCs remains inside a culture vessel and accumulates during the first 24 hours in the cell supernatant. In an organism the IL-12 released from a DC immediately diffuses away. The microenvironment of the DC/T-cell interaction and the immunological synapse is devoid of IL-12 and no IL-12 mediated immune modulation is possible. If T-cells are added to a culture of DCs that had

> the chance to accumulate IL-12 for 24 hours in the supernatant, effects may be observed that might be attributed to accumulated but not freshly secreted IL-12 and which in vivo would never occur 24 hours after exposure to the maturation stimulus.

Thus, the presence of residual IL-12 might be responsible for some level of T-cell stimulation *in vitro*, but would not have the same effect *in vivo*. One of skill in the art following Bosch would not achieve the effect of the present invention, and would have no reason to expect that timing was a critical element for IFN-γ/LPS stimulation based on Bosch and Kalinski, as discussed above. Accordingly, Applicants submit that the present invention provides unexpected results which overcome any showing of prima facie obviousness that may have been established.

The state of the art demonstrates that one of skill in the art would not find the present invention obvious, even to this day.

Dr. Germeraad presents a review of the state of the art, and suggests that only 14 of the over 1000 papers addressing Dendritic cells even mention LPS. He also indicates that in clinical trials, only 2 papers mention the use of LPS. Furthermore, "about 90% of clinical trials that investigate DCs for cancer treatment do not expose them to any maturation agent. More commonly used maturation agents are "CD40*" (7 listings), "TNF" (8 listings), and "CpG" or "polyIC" (4 listings), two other TLR ligands that have a similar effect on DCs as the interaction of LPS with its ligand TLR4." (Declaration, 1.1.2)

Thus, Dr. Germeraad concludes from the survey of the art that one of skill in the art would not have found the present invention obvious back at the time of filing, and would likely not find it obvious today because the vast majority of investigations focus on other aspects of DC therapies.

2. Bosch, Kalinski, and Asavaroengchai

The Examiner also rejects claim 2 under 35 U.S.C. § 103 as unpatentable over Bosch in view of Kalinski and futher in view of Asavaroengchai. As discussed above, Applicants submit that teachings of Bosch and Kalinski do not render the presently claimed method obvious. Asavroengchai does not remedy any of the deficiencies of Bosch and Kalinski with regard to

either the maturation factors or the maturation time. Thus, one of skill in the art would not have found the claimed method obvious. Accordingly, Applicants request that the Examiner withdraw the rejection of claim 2.

3. Bosch, Kalinski, Rieser, and Felzmann (2000)

The Examiner rejects claims 6-8 under 35 U.S.C. § 103 as unpatentable over Bosch, Kalinski, Rieser (of record) and Felzmann (2000)(of record). As discussed above, Applicants submit that teachings of Bosch and Kalinski do not render the presently claimed method obvious. The addition of Rieser and Felzmann (2000) does not remedy any of the deficiencies of Bosch and Kalinski with regard to either the maturation factors or the maturation time. Thus, one of skill in the art would not have found the claimed method obvious. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above remarks, Applicants request the Examiner withdraw all rejections.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By

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Attachments: Declaration of Dr. Germeraad

Information Disclosure Statement